

Lugol Iodine Staining Test in Assessing Disease Free Margins in Tonsillar Cancer

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The carcinoma of the tonsil represents 10-15% of the total of malignant tumors in the oral cavity, having a predilection for males and the great majority is represented by squamous cell carcinomas. In order to improve the long term results of oncologic treatment for patients with tonsillar malignancies early diagnosis and disease free margins during surgery are mandatory. These can be obtained using lugol iodine staining during resection surgery for malignant tumors of the tonsil. This method has been shown to be effective, easy to use, cheap and safe.

Keywords: *lugol iodine, tonsil, carcinoma*

Malignant tumors of the oral cavity represent 5% of all malignant tumors and can affect the lip, the tongue, the floor of the mouth, the buccal mucosa, the soft palate, the tonsils and the mandible and maxilla [1]. Squamous cell carcinoma is the most frequent type of malignancy found in the oral cavity, accounting for up to 95% [2,3].

The carcinoma of the tonsil represents 10-15% of total malignant tumors in the oral cavity, have a predilection for male (4:1 is the male: female ratio) especially between the 6th -8th decade of life and the great majority is represented by squamous cell carcinomas [1,4]. These patients often present a history of alcohol and tobacco abuse, human papilloma virus [5-8]. Due to the lack of symptoms in the early stages of the disease the patients report to medical examination late, in advanced stages, when the prognosis is poor despite multimodal oncologic treatment (surgery, radiotherapy, chemotherapy). The most common symptoms in malignancies of the tonsils are: pain on swallowing, characteristic type of speech, presence of an enlarged tonsil or ulcer on the tonsil with no tendency to healing, oral fetor and bloodstained sputum. Any type of lesion in the oral cavity (including tonsils) that persist more than 3 weeks must be assessed by the ENT specialist.

After local, classical examination that includes bucopharyngoscopy with inspection of the oral cavity, palpation of the suspected lesion, an endoscopic examination of the pharynx with rigid or flexible optics should be performed.

Imagistic examination - CT or MRI - should be performed before any surgical maneuver is planned. It is important to have an imagistic assessment of the cervical lymph nodes in order to obtain an accurate TNM staging of the tumor.

After all these information are gathered, a biopsy sampling should be taken in order to establish the correct histologic diagnosis of the tumor. The next step is to elaborate a treatment plan based on the type of tumor, its grading and its TNM staging. For oral malignancies the best results are obtained with multimodal treatment (surgery, radiotherapy, chemotherapy) carried out by multidisciplinary medical teams (ENT surgeon, oncologist, radiotherapist, nutrition specialist).

In order to improve the long term results of oncologic treatment for patients with oral (including tonsil) malignancies early diagnosis and disease free margins during surgery are mandatory. In the past years new examination techniques have been developed (endoscopy with NBI) and older ones have been improved. Today in vivo staining examination techniques are considered an important element for early diagnosis of malignancies in the head and neck, digestive (especially esophagus and large bowel) and genital (especially cervical) cancers. Methylene blue, toluidine blue and lugol iodine are the most frequent staining agents used for early detection of malignancies and for assessing the surgical resection margins. A recent meta-analysis showed that NBI examination is superior to lugol iodine staining for detection of high-grade dysplasia and squamous cell carcinoma in esophageal malignancies [9,10].

For laryngeal premalignant and malignant lesions contact endoscopy with prior methylene blue staining is an in vivo minimally invasive endoscopic technique with good results in early detection of neoplasia. According to some authors the sensitivity of the method is 79%, the specificity is 79% and the accuracy of the method is 91% [11]. This method has been used, with good results, for assessing the resection margins during CO₂ Laser surgery for glottis cancer [12].

Better results are obtained if two of the aforementioned techniques are applied. For example, the association of contact endoscopy with prior methylene blue staining and NBI improves the assessment of premalignant and malignant lesions of the vocal folds. The authors of the study state that the sensitivity, the specificity and the accuracy of contact endoscopy with methylene blue staining is enhanced when NBI filters are used instead of white light [13].

For oral cavity malignancies toluidine blue staining has been used for assessing the tumor resection margins in order to obtain disease free margins and for early detection of premalignant and malignant lesions in the oral cavity [14]. The results were promising. There is one study that demonstrates 100% sensitivity when using toluidine blue staining for evaluation of resection margins, but the study group is narrow, with only 32 patients enrolled [15].

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Lugol iodine is a glycolophilic staining agent used for assessment of moderate and severe dysplasia and carcinoma in situ of the esophagus. Due to the tissue similarities (stratified non-keratinising glycogen-containing squamous epithelium) between the proximal esophagus and oropharynx, lugol iodine is used more often for the evaluation of lesions of the oral cavity [16]. The normal oropharyngeal cells that contain glycogen become brown in contact with lugol iodine and the dysplastic and cancer cells lack glycogen and remain unstained in contact with lugol [17]. This examination method provides important intraoperative information that can guide the surgeon when performing tumor resection in order to achieve disease free margins of resection.

Experimental part

Although lugol iodine staining method is used for assessing premalignant and malignant lesions of oral cavity and oropharynx there are no studies regarding the tonsillar dysplasia and/or carcinoma.

We have elaborated an examination protocol for evaluation of premalignant and malignant lesions of the tonsils in order to have a better visualization of the tumor (dimensions, margins and limitations of the tumor) during resection surgery.

The first step is a preoperative examination of the oral cavity and oropharynx with thorough inspection of the tonsillar area, base of the tongue and retromolar triangle. Classic buccopharyngoscopy is followed by flexible or rigid endoscopic examination that allows the surgeon to evaluate the inferior pole of the tonsil, base of the tongue, hypopharynx and larynx.

The second step is an intraoperative examination of the tonsillar lesion with lugol iodine staining. The staining technique is quick and easy to apply: the tonsillar region is washed with saline solution, then 3% lugol iodine solution is applied on the tumor and the surrounding tissue and afterward the stained area is washed again with saline solution. After staining the normal tissue becomes dark brown due to the glycogen contained by the normal oropharyngeal cells and the dysplastic or cancer area remain uncolored because these cells are glycogen free.

We have observed a better delimitation of the tumor margins after lugol iodine staining and this was helpful for improvement of disease free margins after surgical resection of the tonsillar carcinoma.

Results and discussions

Today the use of lugol iodine staining for assessment of premalignant and malignant lesions of the oral cavity and disease free resection margins of oral cavity carcinomas is growing. There are many studies that point out the advantages of lugol iodine staining during surgery for oral cavity carcinoma: effective, easy to use, cheap and safe [18,19]. However there is no universally accepted protocol for the staining technique. In the literature different authors have used different concentrations of lugol iodine solution. The most frequent concentrations found are 1%; 3% and 10% [16, 20, 21], but other concentrations were reported as well: 1.5, 2, 5% [22-25]. We are using 3% lugol iodine solution with good results in staining the oral cavity tissue structures.

The importance of disease free resection margins is closely linked to reduced local recurrence and better survival rate. There are studies that state improved survival and lower local recurrence for tongue malignancies after surgical resection and intraoperative staining with lugol iodine [26]. One should have in mind that these good results are for early stage malignancies. The use of lugol

iodine staining method is of great value for premalignant and early stage malignancies (carcinoma in situ, T1 and T2 carcinoma).

Although lugol iodine has been proved to enhance obtaining disease free resection margins for digestive and head and neck malignancies, there are authors who associated two vital dyes (lugol iodine and methylene blue) and their outcomes improved in this situation [27].

Due to the high risk of synchronous and/or metachronous esophageal carcinoma in patients with head and neck malignancies the follow up is very important. We recommend a multidisciplinary team evaluation (ENT surgeon, oncologist, gastroenterologist, nutrition specialist). During follow up the patient needs clinical, endoscopic and imagistic examination. Any suspicious area in the head and neck and/or esophagus must be assessed and biopsy sampling must be obtained. Lugol iodine staining for esophageal lesions is strongly recommended due to its good results in early detection of high-grade dysplasia and early stage carcinoma [28].

Conclusions

Lugol iodine staining is an in vivo examination method used to better evaluate the premalignant and malignant lesions of oral cavity and oropharynx and to improve intraoperative disease free resection margins. This method has multiple advantages; it is effective, easy to use, cheap and safe. Taking into consideration all these aspects we consider that lugol iodine staining should be introduced in every day practice and should be used for all the patients at risk for oral cavity malignancies.

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